diagnosis or assess the efficacy of treatment routines. Magnevist® (Gd-DTPA) and a few other gadolinium-containing MR contrast agents have been used for this purpose, but limitations associated with the dosage and cost of commercially available MR contrast agents have prevented widespread use. Further, these agents would confer no obvious benefit to US imaging due to their low compressibility and the high concentrations required in order to provide effective US imaging.

Perfluorocarbon emulsions have been evaluated for contrast image enhancement. Perflubron (perfluorooctyl bromide, "PFOB") emulsified with egg yolk lecithin has been tested for use in US (due to its high density), MR (fluorine nuclei imaging or as a signal void for hydrogen nuclei imaging) and CT imaging (due to its bromine atom). However, neither fluorine MR imaging nor signal void imaging have found widespread use in hospital or clinical practice, where T_1 (and to a lesser extent, T_2) imaging of protons is typical. Also, PFOB is less dense radiographically, i.e. less radio opaque than iodine-based CT contrast agents, making larger doses necessary in order to achieve adequate x-ray attenuation.

Despite the significance of contrast agents in medical diagnostics and the ever-present need for correlative studies, no single commercially-available contrast agent provides effective, cost-efficient image enhancement utilizing more than one imaging modality.

BRIEF SUMMARY OF THE INVENTION

The invention relates to a new class of contrast agents, namely paramagnetic protein microspheres, for use with multiple imaging modalities. More particularly, this invention relates to gadolinium oxide albumin microspheres ("GOAM"), in both unmodified and surface-modified (including pegylation, antibody attachment, etc.) forms, that are used as

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contrast agents with the more widely used imaging modalities, including US, MR, and CT. In a preferred embodiment, Gd_2O_3 molecules are encapsulated in albumin microspheres. Unmodified and/or surface-modified GOAM of the present invention can function as contrast imaging agents for multiple imaging modalities, such as US, MR and CT.

With respect to US, these microspheres generally have the potential to withstand greater acoustic pressures than prior contrast agents due to the synthesis method used in the present invention. The presence of Gd_2O_3 sequestered within albumin microspheres significantly enhances echogenicity of the protein microspheres. The increased functionality of the GOAM of the present invention as a US contrast agent derives from increased echogenicity due to the effect of Gd_2O_3 on density, compressibility, absorption cross-section, scattering cross-section, and velocity of sound of the albumin microspheres. Additionally, toxicity may be decreased because the overall Gd_2O_3 concentration required for ultrasound image enhancement is reduced due to gadolinium oxide being sequestered within albumin microspheres.

The GOAM of the present invention also can provide enhanced CT imaging due to the high atomic weight and high k-edge of gadolinium. Additionally, GOAM contains multiple Gd_2O_3 particles, each of which are made up of several gadolinium atoms, improving the utility of GOAM as an x-ray attenuation agent for CT.

T_1 and T_2 relaxation enhancement in MR imaging is due to the paramagnetic properties of gadolinium, whose seven unpaired electrons account for its high relaxivity, and the super-paramagnetic and/or ferromagnetic properties of Gd_2O_3, which will be non-specifically sequestered in albumin microspheres, thereby allowing for increased interaction

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with mobile protons, the potential for relaxation via physical rotation of Gd_2O_3 and a decreased tumbling rate of Gd_2O_3 when associated with albumin microspheres. In addition, improved T_1 and T_2 relaxation at lower concentrations of Gd_2O_3 is anticipated due to the association of Gd_2O_3 with a macromolecule, i.e. an albumin microsphere.

GOAM also may be used in therapeutic applications, such as gadolinium neutron capture therapy, because of the high cross-sectional density and high neutron capture rate of gadolinium. Gadolinium has the highest thermal neutron capture cross-section of any known element. GOAM also may be used to encapsulate other therapeutic agents, such as antineoplastic drugs.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a representative image at 40x magnification of prior art unshelled air-filled microbubbles in oil;

Figure 2 is a representative image at 40x magnification of a prior art albumin microsphere;

Figure 3 is a representative image at 40x magnification of a population of Gd_2O_3 albumin microspheres in accordance with the present invention, showing the gadolinium particles inside of the microspheres;

Figure 4a illustrates a cross-section of a plastic tube taken at one end of the tube;

Figure 4b is a representative image of the plastic tube of Figure 4a using B-mode ultrasound of oil;

Figure 4c is a representative image of the plastic tube of Figure 4a using B-mode ultrasound of air-filled albumin microspheres in oil;

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